Acute and Chronic Nicotinic Interactions with Dopamine Systems and Working Memory Performance[a]

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Nicotine has been found to improve memory performance in a variety of studies (for review see ref. 1). Although this effect is not universally seen, studies have found nicotine to improve memory function in rats, monkeys, and humans. Improvements have been found in normal adults, but also in aged subjects and those with brain lesions. The neural bases for this effect is an active topic of study. Nicotine effects may critically involve interactions with other transmitter systems. We found important interactions of nicotinic systems with dopaminergic systems with regard to working memory performance in the radial-arm maze (RAM).

Nicotine has been found to promote the release of a wide variety of transmitters including dopamine (DA).[2] Nicotinic receptors are well represented in the midbrain dopamine nuclei, the substantia nigra (SN) and ventral tegmental area (VTA).[3–5] Acute nicotine administration increases the activity of DA cells in the substantia nigra and ventral tegmental area and promotes DA release in the striatum,[6–11] whereas nicotinic antagonist administration has been found to inhibit DA release from both striatal and mesolimbic structures.[12,13] However, with chronic administration nicotine-induced DA release becomes diminished.[14] There may even be some reversal of the effect, given that chronic nicotine administration has been found to increase DA receptor binding in the nucleus accumbens.[15] Nicotinic-DA interactions have been found in a variety of neurobehavioral studies.[16] The evidence from our laboratory concerning the importance of nicotine interactions with DA systems with regard to working memory function is the focus of this paper. Differences in nicotinic-DA relationships with acute and chronic nicotine treatment are discussed.

ACUTE MECAMYLAMINE STUDIES

The nicotinic antagonist mecamylamine has significant interactions with both dopaminergic agonists and antagonists with regard to working memory performance in the radial-arm maze. In six different studies we found that a high dose of 10 mg/kg of mecamylamine significantly impairs choice accuracy in the win-shift version of the radial-arm maze test.[17–22] This mecamylamine-induced deficit is reversed by the D_2/D_3 DA agonist quinpirole (FIG. 1), but not by a D_1 agonist SKF 38393.[18] A lower

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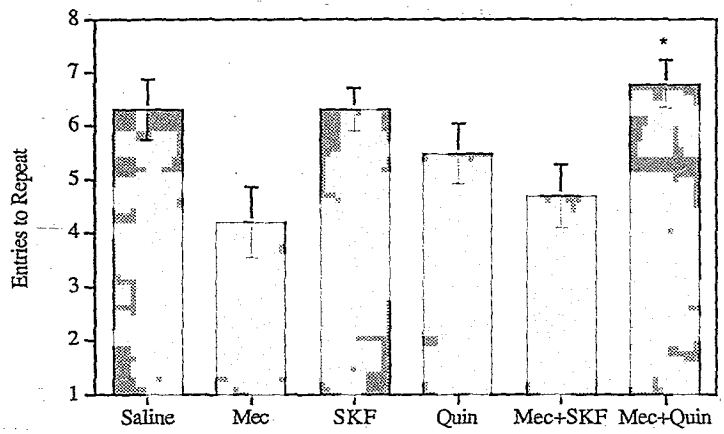

FIGURE 1. Reversal of the mecamylamine-induced radial-arm maze choice accuracy impairment with the D_2/D_3 agonist quinpirole (mean ± SEM). Mec = 10 mg/kg mecamylamine, SKF = 3 mg/kg SKF 38393, Quin = 0.05 mg/kg quinpirole (LY 171555). $^*p < 0.05$ Mec versus Mec + Quin.[18]

dose of 2.5 mg/kg of mecamylamine does not by itself cause a deficit in radial-arm maze choice accuracy, but it does cause a significant choice accuracy deficit when given in conjunction with a low dose of the muscarinic antagonist scopolamine (0.05 mg/kg), which by itself does not cause a significant choice accuracy deficit.[19,20] This combined mecamylamine-scopolamine–induced deficit is also reversed by the D_2/D_3 agonist quinpirole.[20]

The opposite relationship is seen between mecamylamine and DA antagonists. A significant deficit can be elicited by a combination of the subthreshold dose of mecamylamine (2.5 mg/kg) and the mixed D_1/D_2 antagonist haloperidol.[22] The specific D_2 antagonist raclopride has the same effect of potentiating the mecamylamine-induced deficit, whereas addition of the D_1 antagonist SCH 23390 to this dose of mecamylamine has no significant effect.[23] Thus, D_2 receptors appear to have a consistent interaction with the nicotinic antagonist mecamylamine, with an agonist reversing the mecamylamine-induced memory deficit and an antagonist potentiating it. In contrast, D_1 receptors appear to have little interactive effect with mecamylamine.

ACUTE NICOTINE STUDIES

In several studies, we found that acute administration of 0.2 mg/kg of nicotine significantly improves working memory performance in the radial-arm maze.[24–26] This acute nicotine-induced improvement in choice accuracy is reversed by concurrent acute administration of the nicotinic antagonist mecamylamine or the muscarinic antagonist scopolamine.[25] The acute nicotine effect is not as robust as the chronic nicotine effect. In some experiments significant improvements were not seen with the 0.2 mg/kg dose when given alone. However, when the positive effects of acute nicotine are less obvious, they can be made more apparent by co-administra-

tion of dopaminergic agonists. The D_1/D_2 agonist pergolide[27] and the D_2/D_3 agonist quinpirole[26] (FIG. 2) both have mutually potentiating effects when given together with acute doses of 0.2 mg/kg of nicotine. Interestingly, we recently found that this dose of nicotine is effective in attenuating a choice accuracy deficit elicited by the D_1 agonist SKF 38393.[26] Thus, like the nicotinic antagonist mecamylamine, nicotine has significant interactions with dopaminergic drugs. The receptor subtype breakdown is not as clear with nicotine as it is with mecamylamine. As expected, nicotine had a mutually potentiating effect with quinpirole, which effectively reversed the mecamylamine-induced deficit. However, a significant interaction of nicotine with the D_1 agonist SKF 38393 was also found, which did not have a significant interaction with mecamylamine.

ACUTE LOCAL INFUSION STUDIES

Recently we began a series of studies of the effects of nicotinic drugs infused into the ventricles and local brain regions which are the sources or targets of DA systems. Intracerebroventricular (i.c.v.) infusion of nicotine significantly improved choice accuracy performance in rats with little training on the radial-arm maze. In rats trained to high levels of performance no such improvement was detected. However, in this set of rats nicotine was effective in reversing the impairment in performance caused by i.c.v. infusion of the nicotinic antagonist mecamylamine.[28]

Our initial study[29] examined the effects of local infusions of nicotinic agonist and antagonist drugs into the SN and VTA. Mecamylamine infused into either the SN or

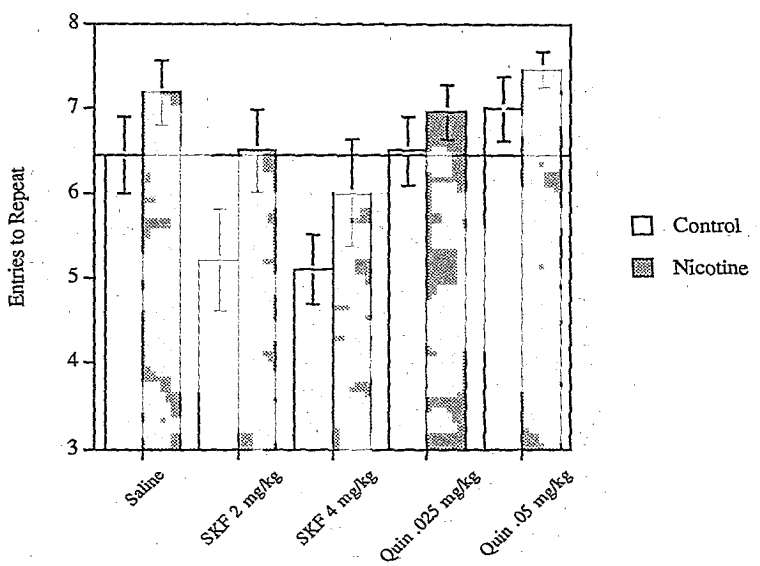

FIGURE 2. Additive effects of nicotine-induced radial-arm maze choice accuracy improvement with the effect of the D_2/D_3 agonist quinpirole and attenuation of the deficit caused by the D_1 agonist SKF 38393 (mean ± SEM).[26]

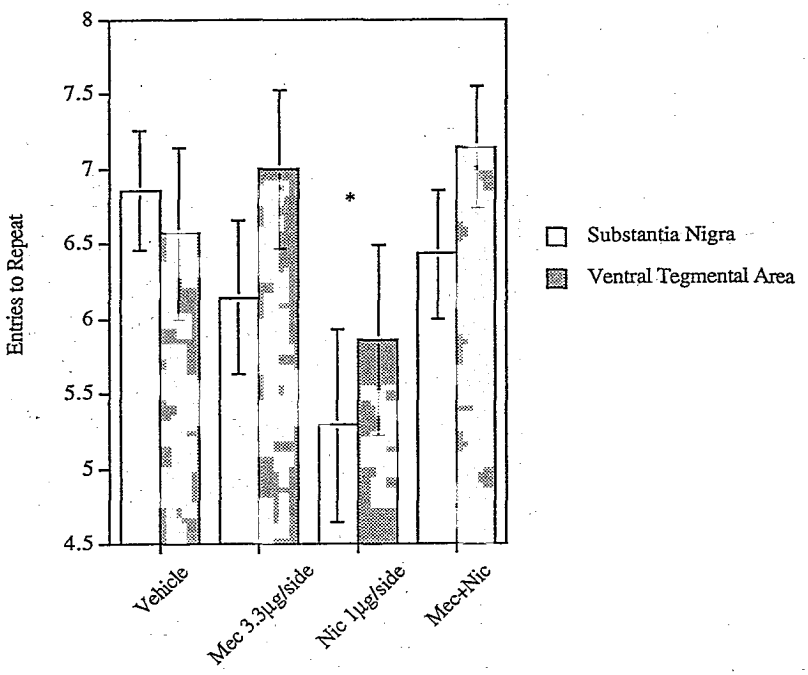

FIGURE 3. Local infusion of nicotine and mecamylamine into the substantia nigra and ventral tegmental area: Effects on choice accuracy in the radial-arm maze (mean ± SEM). $^*p < 0.025$ versus vehicle and Nic + Mec.[29]

VTA significantly impaired choice accuracy in the radial-arm maze. Interestingly, both nicotine and the nicotinic agonist cytisine also showed signs of impairing choice accuracy. This may have been due to the local high concentrations causing desensitization, depolarization blockade or excessive stimulation of the nicotinic receptors in these areas. The results of the combination nicotine-mecamylamine experiment suggest that this may be true. Mecamylamine was effective in significantly reducing the nicotine-induced deficit (FIG. 3). In this same study we did not find any evidence of effects of local infusions of the muscarinic antagonist scopolamine or the muscarinic agonist pilocarpine.

CHRONIC SYSTEMIC STUDIES

We conducted seven different experiments examining the effect of chronic subcutaneous infusion of nicotine (approximately 12 mg/kg/day) via a glass and Silastic pellet or an osmotic minipump. We consistently found that chronic nicotine administration significantly improves memory performance in the radial-arm maze (FIG. 4).[21,30–33] This effect is reversed by concurrent administration of chronic mecamylamine.[32] Acute challenge with mecamylamine during the course of chronic nicotine causes an overall decline in choice accuracy in control and nicotine groups,

but the enhanced performance of the nicotine group relative to controls is preserved.[21] In contrast, we found that acute administration with the muscarinic acetylcholine antagonist scopolamine eliminated the chronic nicotine-induced improvement in choice accuracy.

We have not found concurrent manipulations of D_2 DA receptors to affect significantly the chronic nicotine-induced improvement in choice accuracy. Chronic concurrent administration of either the D_2 agonist quinpirole or the D_2 antagonist raclopride had no discernible effect on the chronic nicotine-induced improvement of choice accuracy. Acute challenge with a range of doses of quinpirole likewise had no significant effect on the chronic nicotine-induced improvement in radial-arm maze choice accuracy. This stands in contrast to the significant interactions we saw between acute nicotine and quinpirole,[26] as well as the significant interactions between acute mecamylamine and both quinpirole and raclopride.[18,23]

LESION STUDIES

Chronic nicotine administration is effective in reversing the radial-arm maze working memory impairments caused by knife-cut lesions of the medial basalocortical projection or the fimbria-fornix, which connects the septum with the hippocampus. This points to the possible therapeutic use of chronic nicotine, but it also gives important information concerning the critical neural substrates for the chronic nicotine-induced improvement. Apparently, neither of these pathways is necessary for the chronic nicotine effects inasmuch as the effect was still seen in the lesioned rats. It may be the case that at least one of the lesioned pathways must be intact for the chronic nicotine-induced memory improvement or, alternatively, other pathways

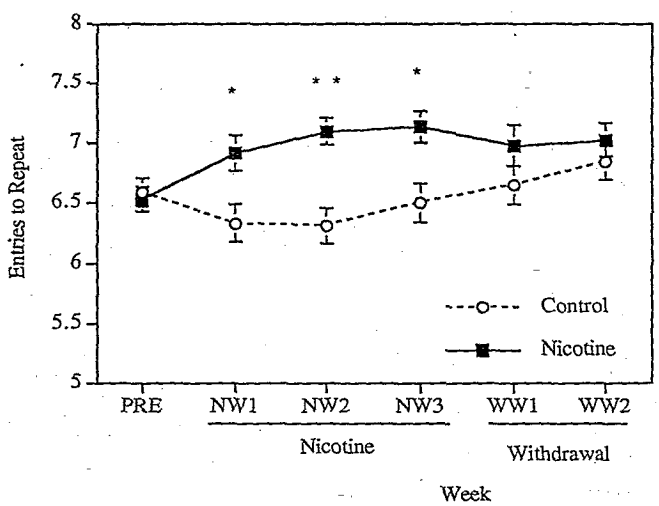

FIGURE 4. Effects of chronic nicotine administration (SC infusions of approximately 12 mg/kg/day) on choice accuracy in the radial-arm maze, averaged over seven experiments (mean ± SEM). During administration of nicotine: Control $n = 60$, nicotine $n = 63$; after withdrawal: Control $n = 51$, nicotine $n = 54$. $^*p < 0.01$, $^{**}p < 0.001$ control versus nicotine.

may subserve the nicotine effect. Interestingly, similar to the therapeutic effect of chronic nicotine, repeated doses of quinpirole also are effective in attenuating the radial-arm maze working memory deficit caused by knife-cut lesions of the medial basalocortical projection.[34] However, simple similarity of effect does not imply common mechanisms of action.

CONCLUSIONS

Nicotinic systems have direct interactions with dopaminergic systems which are important for the acute effects of nicotinic agonist and antagonist manipulations. D_2 receptors seem to be particularly important in this regard. In contrast, chronic nicotine-induced working memory improvement in the radial-arm maze seems to be relatively impervious to concurrent D_2 agonist or antagonist manipulations. The improvement is still seen after lesions to the basalocortical or septohippocampal pathways. Chronic mecamylamine co-administration does prevent the nicotine-induced improvement, but acute mecamylamine challenge does not reverse it. The only other manipulation we found to reverse the chronic nicotine-induced memory improvement is acute challenge with the muscarinic antagonist scopolamine. Nicotinic stimulation is necessary for the induction of the effect but not for the expression of it. In contrast, muscarinic stimulation may be necessary for the expression of the chronic nicotine-induced memory improvement.

Both acute and chronic nicotine administration improve memory performance in the win-shift working memory radial-arm maze task. The involvement of interactions with dopaminergic systems seems to be different for each.

SUMMARY

Nicotine has been found to improve memory performance in a variety of tests in rats, monkeys, and humans. Interactions of nicotinic systems with dopamine (DA) systems may be important for this effect. We conducted a series of studies of nicotinic agonist and antagonist interactions with DA systems using rats in a win-shift working memory task in the radial-arm maze. The working memory deficit caused by the nicotinic antagonist mecamylamine was potentiated by the D_1/D_2 DA antagonist haloperidol and the specific D_2 antagonist raclopride. In contrast, the mecamylamine-induced deficit was reversed by co-administration of the D_2/D_3 agonist quinpirole. Nicotine also has significant interactions with dopamine drugs with regard to working memory performance in the radial-arm maze. The DA agonist pergolide did not by itself improve radial-arm maze memory performance, but when given together with nicotine it produced an elevated dose-dependent increase in choice accuracy. The D_1 agonist SKF 38393 significantly impaired radial-arm maze choice accuracy. Nicotine was effective in reversing this deficit. When given together with nicotine, the D_2/D_3 agonist quinpirole improved RAM choice accuracy relative to either drug alone. Acute local infusion of mecamylamine to the midbrain DA nuclei effectively impairs working memory function in the radial-arm maze. In contrast to acute nicotinic manipulations, considerably less evidence exists that the effects of chronic nicotine administration are influenced by DA systems. This may be an example of the different neural substrates that underlie the memory improvement caused by acute and chronic nicotine.

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